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L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:722915 CAPLUS
DOCUMENT NUMBER: 141:218961
TITLE: **Cannabinoid receptor** inverse agonists as therapeutic agents for non-immediate-type allergic diseases
INVENTOR(S): Iwamura, Hiroyuki; Ueda, Yoshifumi
PATENT ASSIGNEE(S): Japan Tobacco Inc., Japan
SOURCE: U.S. Pat. Appl. Publ., 51 pp., Cont.-in-part of U.S. Ser. No. 375,057.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004171613	A1	20040902	US 2003-734577	20031215
WO 2003061699	A1	20030731	WO 2002-JP13806	20021227
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003232855	A1	20031218	US 2003-375057	20030228

PRIORITY APPLN. INFO.:		
JP 2001-396981	A	20011227
WO 2002-JP13806	A1	20021227
US 2003-375057	A2	20030228

AB Therapeutic agents are provided for non-immediate-type allergic diseases that comprise, as an active ingredient, a **cannabinoid receptor** modulator, particularly that selectively acts on **peripheral cell** type **cannabinoid receptors** (CB2), and more particularly an **inverse agonist**. The invention provides therapeutic agents for non-immediate-type allergic diseases which comprises a **cannabinoid receptor** modulator, particularly an **inverse agonist** that selectively acts on **peripheral cell** type **cannabinoid receptors**, specifically N-(benzo[1,3]dioxol-5-yl methyl)-7-methoxy-2-oxo-8-pentyloxy-1,2-dihydroquinoline-3-carboxamide or such, or pharmaceutically acceptable salt thereof. The therapeutic agents of the invention are effective e.g. against intractable allergic diseases, such as asthma and atopic dermatitis.

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=> d ibib abs 1-21

L10 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:242503 CAPLUS
DOCUMENT NUMBER: 142:445879
TITLE: 2-Arachidonyl glycerol inhibits the immunological activation of human basophils and of guinea pig mast cells
AUTHOR(S): Vannacci, A.; Giannini, L.; Zagli, G.; Pierpaoli, S.; Marzocca, C.; Passani, M. B.; Masini, E.; Mannaioni, P. F.
CORPORATE SOURCE: Department of Preclinical and Clinical Pharmacology, University of Florence, Italy
SOURCE: Allergy Frontiers and Futures, Proceedings of the Symposium of the Collegium Internationale Allergologicum, 24th, Southampton, Bermuda, Nov. 1-7, 2002 (2004), Meeting Date 2002, 110-112. Editor(s): Bienenstock, John; Ring, Johannes; Togias, Alkis G. Hogrefe & Huber Publishers: Cambridge, Mass. CODEN: 69GPMM; ISBN: 0-88937-279-9
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The endogenous cannabinoid 2-arachidonyl glycerol (2AG) may exert receptor-mediated actions on the immune system through the **peripheral** cannabinoid CB2 receptor, located in the spleen, macrophages, lymphoid tissue, and mast cells. Here we report on the effect of 2AG and nitric oxide on the modulation of the immunol. activation of guinea pig mast cells and of human basophils. Partially purified human basophils from healthy donors and purified mast cells from actively sensitized guinea pigs were stimulated in vitro in the absence and in the presence of the drugs under study. 2AG significantly decreased the immunol. release of histamine from guinea pig mast cells and human basophils in a dose-dependent fashion. The **agonist** also inhibited CD63 expression on human basophils challenged with anti-IgE. These inhibitory effects were reverted by the CB2 antagonist SR144528 and by the nitric oxide synthase inhibitor L-NAME, both on human basophils and on guinea pig mast cells.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:121066 CAPLUS
DOCUMENT NUMBER: 142:212370
TITLE: PDE10a inhibitors for treating diabetes and related disorders
INVENTOR(S): Sweet, Laurel
PATENT ASSIGNEE(S): Bayer Pharmaceuticals Corporation, USA
SOURCE: PCT Int. Appl., 28 pp. CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005012485	A2	20050210	WO 2004-US24073	20040727
WO 2005012485	A3	20050414		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-491730P P 20030731

AB The methods of the invention relate to the treatment of diabetes, including type 2 diabetes, and related disorders by administration of a PDE10A inhibitor. Such PDE10A inhibitors may be administered in conjunction with alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, hepatic glucose output lowering compds., β-3 **agonist**, or insulin. Such PDE10A inhibitors may also be administered in conjunction with body weight reducing agents. Further methods of the invention relate to stimulating insulin release from pancreatic cells, for example, in response to an elevation in blood glucose concentration, by administration of a PDE10A inhibitor.

L10 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1038662 CAPLUS
DOCUMENT NUMBER: 142:23402
TITLE: Methods of making cannabinoids derivatives and uses thereof.
INVENTOR(S): Moore, Bob M.; Ferreira, Antonio M.; Krishnamurthy, Mathangi
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 44 pp. CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004242593	A1	20041202	US 2004-850588	20040520
WO 2004113320	A1	20041229	WO 2004-US15885	20040520

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-472316P P 20030520

OTHER SOURCE(S): CASREACT 142:23402; MARPAT 142:23402
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB 1'-Substituted cannabinoid derivs. I [X = CMe2, C(Y(CH2)nY), CH2, C(:O), X = X1, X2; Y = O, S; R1 = C3-8-cycloalkyl, thienyl, furanyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, biphenyl, 2-naphthyl, thiazolyl, benzothiazolyl, methyltetrazolyl, Ra, 3-R11-cyclobutyl, 3-R11-cyclopentyl, 3-R11-4-R12-cyclohexyl, 3-R11-4-R12-5-R13-cycloheptyl, 4-R11-5-R12-6-R13-cyclooctyl; R2, R3 = Me (for Δ8-/Δ9-THC derivs.); R2, R3 = C1-3-alkyl, C1-3-alkanol (for Δ6a,10a-THC derivs.); R4 = Me, CH2OH, (CH2)mCO2H, (CH2)mCHO (for Δ6a,10a-THC derivs.); R4 = Me (for Δ6a,10a-THC derivs.); R5 = H, OH, OMe, OEt; R6 = R10 = H, OH, C1-6-alkyl, halo, NH2, (C1-2-alkyl)amino, di(C1-2-alkyl)amino, amido, (C1-2-alkyl)amido, CN, NO2, C1-6-alkoxy, C1-6-hydroxyalkyl, CO2-(C1-6-alkyl), C(:O)-(C1-6-alkyl), SO-(C1-6-alkyl), SO2-(C1-6-alkyl); one of R11 - R13 = C1-6-alkyl, C1-6-alkoxy, F, Cl (the others are optionally H); n = 2 - 4; m = 0, 1; dashed lines optional double bonds] of Δ8-tetrahydrocannabinol (Δ8-THC), Δ9-tetrahydrocannabinol (Δ9-THC), and Δ6a,10a-tetrahydrocannabinol (Δ6a,10a-THC) that have affinity for the **cannabinoid receptor** type-1 (CB-1) and/or

L10 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
cannabinoid receptor type-2 (CB-2) are described. The method of prepn. of Δ8- and Δ9-tetrahydrocannabinol derivs. comprises reacting intermediate 5-R1XC6H3(OH)2-1,3 with menthols II or III; while the prepn of Δ6a,10a-tetrahydrocannabinol derivs. comprises cyclocondensation of benzenediol deriv. IV; alternatively I can be prepd. via cyclocondensation of 5-R1XC6H3(OH)2-1,3 with Et 2-oxo-4-methylcyclohexanecarboxylatefollowed by reaction of the resulting lactone V with Grignard reagents, ZMgI (Z = R2, R3). Thus, gem-dimethylphenyl-Δ8-THC (V) was prepd. from 3,5-(MeO)2C6H3CHO via Grignard reaction with PhMgBr, PCC oxidn., geminal dimethylation with Me2Zn/TiCl4, O-demethylation with BBr3 and cyclocondensation with cis-p-menth-2-ene-1,8-diol. Compds. having activity as either agonists or antagonists of the CB-1 and/or CB-2 receptors can be used for treating CB-1 or CB-2 mediated conditions. The cytotoxicity of V was detd. [IC50 = 8 μM within 5 h vs. C6 glioma cells].

L10 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:292673 CAPLUS
DOCUMENT NUMBER: 140:369035
TITLE: Cultured rat microglial cells synthesize the endocannabinoid 2-arachidonylglycerol, which increases proliferation via a CB2 receptor-dependent mechanism
AUTHOR(S): Carrier, Erica J.; Kearn, Christopher S.; Barkmeier, Andrew J.; Breese, Nicole M.; Yang, Wenqi; Nithipatikom, Kasem; Pfister, Sandra L.; Campbell, William B.; Hillard, Cecilia J.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, WI, 53226-0509, USA
SOURCE: Molecular Pharmacology (2004), 65(4), 999-1007
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Microglia, as phagocytes and antigen-presenting cells in the central nervous system, are activated in such disease processes as stroke and multiple sclerosis. Because **peripheral** macrophages are capable of producing endocannabinoids, the authors have examined endocannabinoid production in a macrophage-colony stimulating factor (M-CSF)-dependent rat microglial **cell** line (RTMGL1) using reversed phase HPLC and liquid chromatog.-mass spectroscopy. The authors determined that cultured microglial cells produce the endocannabinoid 2-arachidonylglycerol (2-AG) as well as anandamide in smaller quantities. When 2-AG, but not anandamide, is added exogenously, RTMGL1 microglia increase their proliferation. This increased proliferation is blocked by an antagonist of the CB2 receptor N-[(1S)-endo-1,3,3-trimethyl bicyclo heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide (SR144528) and mimicked by the CB2 receptor-specific **agonist** 1,1-dimethylbutyl-1-deoxy-Δ9-tetrahydrocannabinol (JWH133). Accompanying the increase in proliferation seen with 2-AG is an increase in active ERK1 that is also blocked with SR144528. The RTMGL1 microglial cells, which exist in a primed state, express the CB1 and CB2 receptors as demonstrated by reverse transcription-polymerase chain reaction and immunostaining. The CB2 receptor in untreated cells is expressed both at the **cell** surface and internally, and exposure of the cells to 2-AG significantly increases receptor internalization. These data suggest that 2-AG activation of CB2 receptors may contribute to the proliferative response of microglial cells, as occurs in neurodegenerative disorders.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:955404 CAPLUS
DOCUMENT NUMBER: 140:104702
TITLE: The CB1/VR1 **agonist** arvanil induces apoptosis through an FADD/caspase-8-dependent pathway
AUTHOR(S): Sancho, Rocio; de la Vega, Laureano; Appendino, Giovanni; Di Marzo, Vincenzo; Macho, Antonio; Munoz, Eduardo
CORPORATE SOURCE: Departamento de Biologia Celular, Fisiologia e Inmunologia, Universidad de Cordoba, Facultad de Medicina, Cordoba, 14004, Spain
SOURCE: British Journal of Pharmacology (2003), 140(6), 1035-1044
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 1 Arvanil (N-arachidonoylvanillamine), a nonpungent capsaicin-anandamide hybrid mol., has been shown to exert biol. activities through VR1/CB1-dependent and -independent pathways. The authors have found that arvanil induces dose-dependent apoptosis in the lymphoid Jurkat T-**cell** line, but not in **peripheral** blood T lymphocytes. Apoptosis was assessed by DNA fragmentation through **cell** cycle and TUNEL analyses. 2 Arvanil-induced apoptosis was initiated independently of any specific phase of the **cell** cycle, and it was inhibited by specific caspase-8 and -3 inhibitors and by the activation of protein kinase C. In addition, kinetic anal. by Western blots and fluorometry showed that arvanil rapidly activates caspase-8, -7 and -3, and induces PARP cleavage. 3 The arvanil-mediated apoptotic response was greatly inhibited in the Jurkat-FADDDN **cell** line, which constitutively expresses a neg. dominant form of the adapter mol. Fas-associated death domain (FADD). This **cell** line does not undergo apoptosis in response to Fas (CD95) stimulation. 4 Using a cytofluorimetric approach, the authors have found that arvanil induced the production of reactive oxygen species (ROS) in both Jurkat-FADD+ and Jurkat-FADDDN **cell** lines. However, ROS accumulation only plays a residual role in arvanil-induced apoptosis. 5 These results demonstrate that arvanil-induced apoptosis is essentially mediated through a mechanism that is typical of type II cells, and implicates the death-inducing signaling complex and the activation of caspase-8. This arvanil-apoptotic activity is TRPV1 and CB-independent, and can be of importance for the development of potential anti-inflammatory and antitumoral drugs.
REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:757550 CAPLUS
DOCUMENT NUMBER: 139:255382
TITLE: Methods of treating diabetes using PDE11a inhibitors
INVENTOR(S): Vasavada, Haren
PATENT ASSIGNEE(S): Bayer Pharmaceuticals Corporation, USA
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003077949	A2	20030925	WO 2003-US8132	20030314
WO 2003077949	A3	20040325		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2477832	AA	20030925	CA 2003-2477832	20030314
EP 1496940	A2	20050119	EP 2003-716641	20030314
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003008415	A	20050215	BR 2003-8415	20030314

PRIORITY APPLN. INFO.: US 2002-364697P P 20020314
US 2002-389036P P 20020613
WO 2003-US8132 W 20030314

AB Methods of the invention relate to treatment of diabetes, particularly type 2 diabetes, and related disorders by administration of a PDE11A inhibitor. Such PDE11A inhibitors may be administered in conjunction with alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, hepatic glucose output lowering compds., beta3 **agonist** or insulin. Such PDE11A inhibitors may also be administered in conjunction with body weight reducing agents. Further methods of the invention relate to stimulating insulin release from pancreatic cells, particularly in response to an elevation in blood glucose concentration, by administration of a PDE11A inhibitor.

L10 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:164187 CAPLUS
DOCUMENT NUMBER: 135:439
TITLE: Inhibitory effects of SR141716A on G-protein activation in rat brain
AUTHOR(S): Sim-Selley, L. J.; Brunk, L. K.; Selley, D. E.
CORPORATE SOURCE: Department of Pharmacology and Toxicology and Institute for Drug and Alcohol Studies, Virginia Commonwealth University Medical College of Virginia, Richmond, VA, 23298, USA
SOURCE: European Journal of Pharmacology (2001), 414(2/3), 135-143
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride (SR141716A), a cannabinoid CB1 receptor antagonist, has inverse **agonist** effects in cannabinoid CB1 receptor-expressing **cell** lines, brain and **peripheral** organs. These studies characterized SR141716A-inhibited G-protein activity by measuring [35S]GTPγS binding. Maximal inhibition of basal [35S]GTPγS binding in cerebellar membranes was 50%. The EC50 value for inhibition of [35S]GTPγS binding was 4.4 μM, whereas the Ke for inhibition of R(+)-[2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl)methanone mesylate (WIN 55,212-2)-stimulated [35S]GTPγS binding was 0.6 nM. [35S]GTPγS autoradiog. was used to examine the regional specificity of SR141716A inhibition. SR141716A inhibited basal [35S]GTPγS binding in all regions examined, with inhibition ranging from approx. 20% in caudate-putamen to 40% in hippocampus. These studies demonstrate that SR141716A is a competitive antagonist at nanomolar concns., whereas it inhibits basal receptor-mediated G-protein activity at micromolar concns. These data suggest that the apparent inverse **agonist effect** is either not cannabinoid CB1 receptor-specific or that SR141716A is binding to different sites on the cannabinoid CB1 receptor to produce inverse **agonist** vs. competitive antagonist effects.
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:87292 CAPLUS
DOCUMENT NUMBER: 134:275495
TITLE: In vitro and in vivo pharmacological characterization of JTE-907, a novel selective ligand for cannabinoid CB2 receptor
AUTHOR(S): Iwamura, Hiroyuki; Suzuki, Hidekazu; Ueda, Yoshifumi; Kaya, Tetsudo; Inaba, Takashi
CORPORATE SOURCE: Central Pharmaceutical Research Institute, Japan Tobacco Inc., Osaka, Japan
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2001), 296(2), 420-425
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB JTE-907 [N-(benzo[1,3]dioxol-5-ylmethyl)-7-methoxy-2-oxo-8-pentyloxy-1,2-di hydroquinoline-3-carboxamide] was evaluated in vitro and in vivo as a novel selective ligand for **cannabinoid receptor** of **peripheral** type (CB2). The compound binds with high affinity to human CB2 or mouse CB2 expressed on CHO **cell** membrane and to rat CB2 on splenocytes. The Ki affinities for human, mouse, and rat CB2 were 35.9, 1.55, and 0.38 nM, resp. The selectivity ratio for the CB2 receptors compared with central nervous type receptors (CB1) of human (expressed on CHO cells), and mouse and rat CB1 on cerebellum were 66, 684, and 2760, resp. JTE-907 showed concentration-dependent increase of forskolin-stimulated cAMP production in CHO cells expressing human and mouse CB2 in vitro, i.e., JTE-907 behaved as an inverse **agonist**, which is in contrast to Win55212-2 that reduces cAMP as an **agonist**. JTE-907 dosed orally inhibited carrageenin-induced mouse paw edema dose dependently. The same in vivo effect was observed with other **cannabinoid receptor** ligands such as SR144528, Δ9-tetrahydrocannabinol (THC), and Win55212-2. This is the first report that a CB2-selective inverse **agonist**, JTE-907, has an anti-inflammatory effect in vivo, and how the inverse **agonist** showed the same effect as Win55212-2 and Δ9-THC is discussed.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:392087 CAPLUS
DOCUMENT NUMBER: 133:99812
TITLE: Genomic and functional changes induced by the activation of the **peripheral cannabinoid receptor** CB2 in the promyelocytic cells HL-60. Possible involvement of the CB2 receptor in **cell** differentiation
AUTHOR(S): Derocq, Jean-Marie; Jbilo, Omar; Bouaboula, Monsif; Segui, Michel; Clere, Christophe; Casellas, Pierre
CORPORATE SOURCE: Sanofi-Synthelabo, Montpellier, 34184, Fr.
SOURCE: Journal of Biological Chemistry (2000), 275(21), 15621-15628
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The function of the **peripheral cannabinoid receptor** (CB2), which is mainly expressed on hematopoietic cells, remains an enigma. To decipher its role, the authors used Affymetrix DNA chips to investigate the gene expression profile of the promyelocytic cells HL-60 transfected with the CB2 receptor and activated with the cannabinoid **agonist** CP 55,940. **Agonist** exposure of these cells led to an activation of a mitogen-activated protein kinase cascade and a receptor desensitization, indicating a functional coupling of the transfected receptors. At the genomic level, activation of the CB2 receptors induced an up-regulation of nine genes involved in cytokine synthesis, regulation of transcription, and **cell** differentiation. A majority of them are under the control of the transcription factor NF-κB, whose nuclear translocation was demonstrated. Many features of the transcriptional events, reported here for the first time, appeared to be related to an activation of a **cell** differentiation program, suggesting that CB2 receptors could play a role in the initialization of **cell** maturation. Moreover, the authors showed that CB2-activated wild-type HL-60 cells developed properties usually found in host defense effector cells such as an enhanced release of chemotactic cytokines and an increased motility, characteristic of more mature cells of the granulocytic-monocytic lineage.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:345444 CAPLUS
DOCUMENT NUMBER: 133:99452
TITLE: Immunomodulation by cannabinoids is absent in mice deficient for the cannabinoid CB2 receptor
AUTHOR(S): Buckley, N. E.; McCoy, K. L.; Mezey, E.; Bonner, T.; Zimmer, A.; Felder, C. C.; Glass, M.; Zimmer, A.
CORPORATE SOURCE: NINDS, Basic Neuroscience Program, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: European Journal of Pharmacology (2000), 396(2/3), 141-149
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cannabinoids have immunomodulatory as well as psychoactive effects. Because the central **cannabinoid receptor** (cannabinoid CB1 receptor) is highly expressed in many neuronal tissues and the **peripheral cannabinoid receptor** (cannabinoid CB2 receptor) is highly expressed in immune cells, it has been suggested that the central nervous system effects of cannabinoids are mediated by cannabinoid CB1 receptors and that the immune effects are mediated by cannabinoid CB2 receptors. To test this hypothesis, we have generated the first mouse strain with a targeted mutation in the cannabinoid CB2 receptor gene. Binding studies using the highly specific synthetic **cannabinoid receptor agonist** (-)-cis-3-[2-Hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol ([3H]CP 55,940) revealed no residual cannabinoid binding sites in the spleen of the cannabinoid CB2 receptor knockout mice, while binding in the central nervous system was unchanged. Cannabinoid CB2 receptor knockout mice, which appear healthy, are fertile and care for their offspring. Fluorescence activated **cell** sorting (FACS) anal. showed no differences in immune **cell** populations between cannabinoid CB2 receptor knockout and wild type mice. We investigated the immunomodulatory effects of cannabinoids in cannabinoid CB2 receptor deficient mice using a T **cell** co-stimulation assay. Δ9-Tetrahydrocannabinol inhibits helper T **cell** activation through macrophages derived from wild type, but not from knockout mice, thus indicating that this effect is mediated by the cannabinoid CB2 receptor. In contrast, central nervous system effects of cannabinoids were not altered in these mice. Our results suggest that cannabinoid CB2 receptor-specific ligands may be clin. useful in the modulation of macrophage immune function while exhibiting no central nervous system activity. Furthermore, we conclude that the cannabinoid CB2 receptor knockout mouse is a useful animal model in which to study the role of the cannabinoid system in immunoregulation.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:467037 CAPLUS
DOCUMENT NUMBER: 131:237853
TITLE: Regulation of **peripheral cannabinoid receptor** CB2 phosphorylation by the inverse **agonist** SR 144528. Implications for receptor biological responses
AUTHOR(S): Bouaboula, Monsif; Dussossoy, Danielle; Casellas, Pierre
CORPORATE SOURCE: Sanofi Recherche, Montpellier, 34184, Fr.
SOURCE: Journal of Biological Chemistry (1999), 274(29), 20397-20405
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We recently demonstrated that the selective **cannabinoid receptor** antagonist SR 144528 acts as an inverse **agonist** that blocks constitutive mitogen-activated protein kinase activity coupled to the spontaneous autoactivated **peripheral cannabinoid receptor** (CB2) in the Chinese hamster ovary **cell** line stably transfected with human CB2. In the present report, we studied the effect of SR 144528 on CB2 phosphorylation. The CB2 phosphorylation status was monitored by immunodetection using an antibody specific to the COOH-terminal CB2 which can discriminate between phosphorylated and non-phosphorylated CB2 isoforms at serine 352. We first showed that CB2 is constitutively active, phosphorylated, and internalized at the basal level. By blocking autoactivated receptors, inverse **agonist** SR 144528 treatment completely inhibited this phosphorylation state, leading to an up-regulated CB2 receptor level at the **cell** surface, and enhanced cannabinoid **agonist** sensitivity for mitogen-activated protein kinase activation of Chinese hamster ovary-CB2 cells. After acute **agonist** treatment, serine 352 was extensively phosphorylated and maintained in this phosphorylated state for more than 8 h after **agonist** treatment. The cellular responses to CP-55,940 were concomitantly abolished. Surprisingly, CP-55,940-induced CB2 phosphorylation was reversed by SR 144528, paradoxically leading to a non-phosphorylated CB2 which could then be fully activated by CP-55,940. The process of CP-55,940-induced receptor phosphorylation followed by SR 144528-induced receptor dephosphorylation kept recurring many times on the same cells, indicating that the **agonist** switches the system off but the inverse **agonist** switches the system back on. Finally, we showed that autophosphorylation and CP-55,940-induced serine 352 CB2 phosphorylation involve an acidotropic GRK kinase, which does not use Giβγ. In contrast, SR 144528-induced CB2 dephosphorylation was found to involve an okadaic acid and calyculin A-sensitive type 2A phosphatase.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:171080 CAPLUS
DOCUMENT NUMBER: 130:335881
TITLE: Gi protein modulation induced by a selective inverse **agonist** for the **peripheral cannabinoid receptor** CB2: implication for intracellular signalization cross-regulation
AUTHOR(S): Bouaboula, Monsif; Desnoyer, Nathalie; Carayon, Pierre; Combes, Therese; Casellas, Pierre
CORPORATE SOURCE: Sanofi Recherche, Montpellier, Fr.
SOURCE: Molecular Pharmacology (1999), 55(3), 473-480
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **peripheral cannabinoid receptor** (CB2) is a G protein-coupled receptor that is both pos. and neg. coupled to the mitogen-activated protein kinase (MAPK) and cAMP pathways, resp., through a Bordetella pertussis toxin-sensitive G protein. CB2 receptor-transfected Chinese hamster ovary cells exhibit high constitutive activity blocked by the CB2-selective ligand, SR 144528, working as an inverse **agonist**. The authors showed here that in addition to the inhibition of auto-activated CB2 in this model, the authors found that SR 144528 inhibited the MAPK activation induced by Gi-dependent receptors such as receptor-tyrosine kinase (insulin, insulin-like growth factor 1) or G protein-coupled receptors (lysophosphatidic acid), but not by Gi-independent receptors such as the fibroblast growth factor receptor. The authors showed that this SR 144528 inhibitory effect on Gi-dependent receptors was mediated by a direct Gi protein inhibition through CB2 receptors. Indeed, the authors found that through binding to the CB2 receptors, SR 144528 blocked the direct activation of the Gi protein by mastoparan analog in Chinese hamster ovary CB2 **cell** membranes. Furthermore, the authors described that sustained treatment with SR 144528 induced an up-regulation of the cellular Gi protein level as shown in Western blotting as well as in confocal microscopic expts. This up-regulation occurred with a concomitant loss of SR 144528 ability to inhibit the insulin or lysophosphatidic acid-induced MAPK activation. This inverse **agonist**-induced modulation of the Gi strongly suggests that the modulated protein is functionally associated with the complex SR 144528/CB2 receptors, and that the Gi level may account for the heterologous desensitization phenomena.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:746631 CAPLUS
DOCUMENT NUMBER: 130:119939
TITLE: Modulation and functional involvement of CB2 **peripheral cannabinoid receptors** during B-**cell** differentiation
AUTHOR(S): Carayon, Pierre; Marchand, Jean; Dussossoy, Danielle; Derocq, Jean-Marie; Jbilo, Omar; Bord, Annie; Bouaboula, Monsif; Galiegue, Sylvaine; Mondiere, Paul; Penarier, Geraldine; Le Fur, Gerard; Defrance, Thierry; Casellas, Pierre
CORPORATE SOURCE: Immunology Department, Sanofi Recherche, Montpellier, 34184, Fr.
SOURCE: Blood (1998), 92(10), 3605-3615
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two subtypes of G-protein-coupled **cannabinoid receptors** have been identified to date: the CB1 central receptor subtype, which is mainly expressed in the brain, and the CB2 **peripheral** receptor subtype, which appears particularly abundant in the immune system. We investigated the expression of CB2 receptors in leukocytes using anti-CB2 receptor immunopurified polyclonal antibodies. We showed that **peripheral** blood and tonsillar B cells were the leukocyte subsets expressing the highest amount of CB2 receptor proteins. Dual-color confocal microscopy performed on tonsillar tissues showed a marked expression of CB2 receptors in mantle zones of secondary follicles, whereas germinal centers (GC) were weakly stained, suggesting a modulation of this receptor during the differentiation stages from virgin B lymphocytes to memory B cells. Indeed, we showed a clear downregulation of CB2 receptor expression during B-**cell** differentiation both at transcript and protein levels. The lowest expression was observed in GC proliferating centroblasts. Furthermore, we investigated the effect of the cannabinoid **agonist** CP55,940 on the CD40-mediated proliferation of both virgin and GC B-**cell** subsets. We found that CP55,940 enhanced the proliferation of both subsets and that this enhancement was blocked by the CB2 receptor antagonist SR 144528α but not by the CB1 receptor antagonist SR 141716α. Finally, we observed that CB2 receptors were dramatically upregulated in both B-**cell** subsets during the first 24 h of CD40-mediated activation. These data strongly support an involvement of CB2 receptors during B-**cell** differentiation.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:206201 CAPLUS
DOCUMENT NUMBER: 129:3179
TITLE: The endogenous cannabinoid anandamide is a lipid messenger activating **cell** growth via a **cannabinoid receptor**-independent pathway in hematopoietic **cell** lines
AUTHOR(S): Derocq, J.-M.; Bouaboula, M.; Marchand, J.; Rinaldi-Carmona, M.; Segui, M.; Casellas, P.
CORPORATE SOURCE: Sanofi Recherche, Montpellier, 34184, Fr.
SOURCE: FEBS Letters (1998), 425(3), 419-425
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of anandamide, an endogenous ligand for central (CB1) and **peripheral** (CB2) **cannabinoid receptors**, was investigated on the growth of the murine IL-6-dependent lymphoid **cell** line B9 and the murine IL-3-dependent myeloblastic **cell** line FDC-P1. In conditions of low serum level, anandamide potentiated the growth of both cytokine-dependent **cell** lines. Comparison with other fatty acid cannabinoid ligands such as (R)-methanandamide, a ligand with improved selectivity for the CB1 receptor, or palmitylethanolamide, an endogenous ligand for the CB2 receptor, showed a very similar effect, suggesting that **cell** growth enhancement by anandamide or its analogs could be mediated through either receptor subtype. However, several lines of evidence indicated that this growth-promoting effect was **cannabinoid receptor**-independent. First, the potent synthetic cannabinoid **agonist** CP 55940, which displays high affinity for both receptors, was inactive in this model. Second, SR 141716A and SR 144528, which are potent and specific antagonists of CB1 and CB2 receptors resp., were unable, alone or in combination, to block the anandamide-induced effect. Third, inactivation of both receptors by pretreatment of cells with pertussis toxin did not affect the potentiation of **cell** growth by anandamide. These data demonstrated that neither CB1 nor CB2 receptors were involved in the anandamide-induced effect. Moreover, using CB2-transfected Chinese hamster ovary cells, it was demonstrated that after complete blockade of the receptors by the specific antagonist SR 144528, anandamide was still able to strongly stimulate a mitogen-activated protein (MAP) kinase activity, clearly indicating that the endogenous cannabinoid can transduce a mitogenic signal in the absence of available receptors. Finally, arachidonic acid, a structurally related compound and an important lipid messenger without known affinity for **cannabinoid receptors**, was shown to trigger MAP kinase activity and **cell** growth enhancement similar to those observed with anandamide. These findings provide clear evidence for a functional role of anandamide in activating a signal transduction pathway leading to **cell** activation and proliferation via a non-**cannabinoid receptor**-mediated process.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:362889 CAPLUS
DOCUMENT NUMBER: 127:90382
TITLE: Differential effects of CB1 and CB2 agonists on cAMP levels and MAP kinase activation in human **peripheral** blood mononuclear cells
AUTHOR(S): Makda, Ashraff A.; Elmore, Moira A.; Hill, Maxine E.; Stamps, Alasdair; Tejura, Smita; Finnen, Michael J.
CORPORATE SOURCE: Yamanouchi Research Inst., Oxford, OX4 4SX, UK
SOURCE: Biochemical Society Transactions (1997), 25(2), 217S
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors investigated the effects of Δ9-tetrahydrocannabinol (which acts as an **agonist** at CB1 receptors and an antagonist at CB2 receptors) and the endogenous ligand palmitoyl ethanolamine (which acts as an **agonist** at CB2 receptors and an antagonist at CB1 receptors) on cAMP levels and MAP kinase activation in human **peripheral** blood mononuclear cells. While neither cannabinoid affected cAMP levels on their own, Δ9-tetrahydrocannabinol inhibited isoproterenol-induced stimulation of cAMP levels and palmitoyl ethanolamine increased the levels of cAMP produced following isoproterenol treatment. Also, the cells treated with palmitoyl ethanolamine have an active kinase at approx. 90 kDa which is not detectable in the Δ9-tetrahydrocannabinol-treated cells. Δ9-Tetrahydrocannabinol activated ERK 2 rapidly whereas palmitoyl ethanolamine had no effect. Therefore, the effects of Δ9-tetrahydrocannabinol (CB1 **agonist**) and palmitoyl ethanolamine (CB2 **agonist**) on 2 signaling pathways are different.
REFERENCE COUNT: 0 THERE ARE 0 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:193300 CAPLUS
DOCUMENT NUMBER: 126:275345
TITLE: Biosynthesis, release and degradation of the novel endogenous cannabimimetic metabolite 2-arachidonoylglycerol in mouse neuroblastoma cells
AUTHOR(S): Bisogno, Tiziana; Sepe, Nunzio; Melck, Dominique; Maurelli, Stefano; De Petrocellis, Luciano; Di Marzo, Vincenzo
CORPORATE SOURCE: Ist. Chimica Molecole Interesse Biologico, C.N.R., naples, 80072, Italy
SOURCE: Biochemical Journal (1997), 322(2), 671-677
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The monoacylglycerol 2-arachidonoylglycerol (2-AG) has been recently suggested as a possible endogenous **agonist** at **cannabinoid receptors** both in brain and **peripheral** tissues. Here we report that a widely used model for neuronal cells, mouse N18TG2 neuroblastoma cells, which contain the CB1 **cannabinoid receptor**, also biosynthesize, release and degrade 2-AG. Stimulation with ionomycin (1-5 μM) of intact cells prelabeled with [3H]arachidonic acid ([3H]AA) led to the formation of high levels of a radioactive component with the same chromatog. behavior as synthetic stds. of 2-AG in TLC and HPLC analyses. The amts. of this metabolite were negligible in unstimulated cells, and greatly decreased in cells stimulated in the presence of the Ca2+-chelating agent EGTA. The purified component was further characterized as 2-AG by: (1) digestion with Rhizopus arrhizus lipase, which yielded radiolabeled AA; (2) gas chromatog.-MS analyses; and (3) TLC analyses on borate-impregnated plates. Approx. 20% of the 2-AG produced by stimulated cells was found to be released into the incubation medium when this contained 0.1% BSA. Subcellular fractions of N18TG2 cells were shown to contain enzymic activity or activities catalyzing the hydrolysis of synthetic [3H]2-AG to [3H]AA. **Cell** homogenates were also found to convert synthetic [3H]sn-1-acyl-2-arachidonoylglycerols (AcAGs) into [3H]2-AG, suggesting that 2-AG might be derived from AcAG hydrolysis. When compared with ionomycin stimulation, treatment of cells with exogenous phospholipase C, but not with phospholipase D or A2, led to a much higher formation of 2-AG and AcAGs. However, treatment of cells with phospholipase A2 10 min before ionomycin stimulation caused a 2.5-3-fold potentiation of 2-AG and AcAG levels with respect to ionomycin alone, whereas preincubation with the phospholipase C inhibitor neomycin sulfate did not inhibit the effect of ionomycin on 2-AG and AcAG levels. These results suggest that the Ca2+-induced formation of 2-AG proceeds through the intermediacy of AcAGs but not necessarily through phospholipase C activation. By showing for the first time the existence of mol. mechanisms for the inactivation and the Ca2+-dependent biosynthesis and release of 2-AG in neuronal cells, the present paper supports the hypothesis that this cannabimimetic monoacylglycerol might be a physiol. neuromodulator.

L10 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L10 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:296919 CAPLUS
DOCUMENT NUMBER: 125:108041
TITLE: Molecular cloning, expression and function of the murine CB2 **peripheral cannabinoid receptor**
AUTHOR(S): Shire, David; Calandra, Bernard; Rinaldi-Carmona, Murielle; Oustric, Didier; Pessegue, Bernard; Bonnin-Cabanne, Odile; Le Fur, Gerard; Caput, Daniel; Ferrara, Pascual
CORPORATE SOURCE: Sanofi Recherche, Centre de Labege, Labege-Innopole BP 137, 31676, Labege, Fr.
SOURCE: Biochimica et Biophysica Acta (1996), 1307(2), 132-136
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **peripheral cannabinoid receptor**, mCB2, was cloned from a mouse splenocyte cDNA library. The 3.7-kb sequence contains an open reading frame encoding a protein of 347 residues sharing 82% overall identity with the only other known **peripheral** receptor, human CB2 (hCB2) and shorter than hCB2 by 13 amino acids at the C-terminus. Binding expts. with membranes from COS-3 cells transiently expressing mCB2 showed that the synthetic cannabinoid WIN 55212-2 had a 6-fold lower affinity for mCB2 than for hCB2, whereas both receptors showed similar affinities for the agonists CP 55,940, Δ9-THC, and anandamide and almost no affinity for the central receptor- (CB1) specific antagonist SR 141716A. Both hCB2 and mCB2 mediate **agonist** -stimulated inhibition of forskolin-induced cAMP production in CHO **cell** lines permanently expressing the receptors. SR 141716A failed to antagonize this activity in either **cell** line, confirming its specificity for CB1.

L10 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:286872 CAPLUS
DOCUMENT NUMBER: 125:26016
TITLE: The ALIAmide palmitoylethanolamide and cannabinoids, but not anandamide, are protective in a delayed postglutamate paradigm of excitotoxic death in cerebellar granule neurons
AUTHOR(S): Skaper, S. D.; Buriani, A.; Toso, R. Dal; Petrelli, L.; Romanello, S.; Facci, L.; Leon, A.
CORPORATE SOURCE: Cent. Ricerca Biomed.-Ospedale Civile, Researchlife S.c.p.A., Castelfranco Veneto (TV), 31033, Italy
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1996), 93(9), 3984-3989
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The amino acid L-glutamate is a neurotransmitter that mediates fast neuronal excitation in a majority of synapses in the central nervous system. Glutamate stimulates both N-methyl-D-aspartate (NMDA) and non-NMDA receptors. While activation of NMDA receptors has been implicated in a variety of neurophysiol. processes, excessive NMDA receptor stimulation (excitotoxicity) is thought to be primarily responsible for neuronal injury in a wide variety of acute neurol. disorders including hypoxia-ischemia, seizures, and trauma. Very little is known about endogenous mols. and mechanisms capable of modulating excitotoxic neuronal death. Saturated N-acylethanolamides like palmitoylethanolamide accumulate in ischemic tissues and are synthesized by neurons upon excitatory amino acid receptor activation. Here the authors report that palmitoylethanolamide, but not the cognate N-acylamide anandamide (the ethanolamide of arachidonic acid), protects cultured mouse cerebellar granule cells against glutamate toxicity in a delayed postagonist paradigm. Palmitoylethanolamide reduced this injury in a concentration-dependent manner and was maximally effective when added 15-min postglutamate. Cannabinoids, which like palmitoylethanolamide are functionally active at the **peripheral cannabinoid receptor** CB2 on mast cells, also prevented neuron loss in this delayed postglutamate model. Furthermore, the neuroprotective effects of palmitoylethanolamide, as well as that of the active cannabinoids, were efficiently antagonized by the candidate central **cannabinoid receptor** (CB1) **agonist** anandamide. Analogous pharmacol. behaviors have been observed for palmitoylethanolamide (ALIAmides) in downmodulating mast **cell** activation. Cerebellar granule cells expressed mRNA for CB1 and CB2 by in situ hybridization, while two cannabinoid binding sites were detected in cerebellar membranes. The results suggest that (i) non-CB1 **cannabinoid receptors** control, upon **agonist** binding, the downstream consequences of an excitotoxic stimulus; (ii) palmitoylethanolamide, unlike anandamide, behaves as an endogenous **agonist** for CB2-like receptors on granule cells; and (iii) activation of such receptors may serve to downmodulate deleterious cellular processes following pathol. events or noxious stimuli in both the nervous and immune systems.

L10 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:188147 CAPLUS
DOCUMENT NUMBER: 124:277992
TITLE: Structural features of the central cannabinoid CB1 receptor involved in the binding of the specific CB1 antagonist SR 141716A
AUTHOR(S): Shire, David; Calandra, Bernard; Delpech, Monique; Dumont, Xavier; Kaghad, Mourad; Le Fur, Gerard; Caput, Daniel; Ferrara, Pascual
CORPORATE SOURCE: Sanofi Recherche, Centre Labege, Labege, 31676, Fr.
SOURCE: Journal of Biological Chemistry (1996), 271(12), 6941-46
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antagonist SR 141716A has a high specificity for the central CB1 **cannabinoid receptor** and negligible affinity for the **peripheral** CB2 receptor, making it an excellent tool for probing receptor structure-activity relationships. From binding expts. with mutated CB1 and with chimeric CB1/CB2 receptors we have begun to identify the domains of CB1 implicated in the recognition of SR 14176A. Receptors were transiently expressed in COS-3 cells, and their binding characteristics were studied with SR 141716A and with CP 55,940, an **agonist** recognized equally well by the two receptors. The region delineated by the four and fifth transmembrane helixes of CB1 proved to be crucial for high affinity binding of SR 141716A. The CB1 and CB2 2nd extracellular loops, e2, were exchanged, modifications that had no effect on SR 141716A binding in the CB1 variant but that eliminated CP 55,940 binding in both mutants. The replacement of the conserved cysteine residues in e2 of CB2 by serine also eliminated CP 55,940 binding, but replacement of those in CB1 resulted in the sequestration of the mutated receptors in the **cell** cytoplasm. The e2 domain thus plays some role in CP 55,940 binding but none in SR 141716A recognition, binding of the latter clearly implicating residues in the adjoining transmembrane helixes.

L10 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:510487 CAPLUS
DOCUMENT NUMBER: 122:255820
TITLE: Mast cells express a **peripheral cannabinoid receptor** with differential sensitivity to anandamide and palmitoylethanolamide
AUTHOR(S): Facci, L.; Dal Toso, R.; Romanello, S.; Buriani, A.; Skaper, S. D.; Leon, A.
CORPORATE SOURCE: Researchlife, Veneto, 31033, Italy
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1995), 92(8), 3376-80
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mast cells are multifunctional bone marrow-derived cells found in mucosal and connective tissues and in the nervous system, where they play important roles in tissue inflammation and in neuroimmune interactions. Very little is known about endogenous mols. and mechanisms capable of modulating mast **cell** activation. Palmitoylethanolamide, found in **peripheral** tissues, has been proposed to behave as a local autacoid capable of downregulating mast **cell** activation and inflammation. A cognate N-acylamide, anandamide, the ethanolamide of arachidonic acid, occurs in brain and is a candidate endogenous **agonist** for the central **cannabinoid receptor** (CB1). As a second **cannabinoid receptor** (CB2) has been found in **peripheral** tissues, the possible presence of CB2 receptors on mast cells and their interaction with N-acylamides was investigated. Here the authors report that mast cells express both the gene and a functional CB2 receptor protein with neg. regulatory effects on mast **cell** activation. Although both palmitoylethanolamide and anandamide bind to the CB2 receptor, only the former downmodulates mast **cell** activation in vitro. Further, the functional effect of palmitoylethanolamide, as well as that of the active cannabinoids, was efficiently antagonized by anandamide. The results suggest that (i) **peripheral** cannabinoid CB2 receptors control, upon **agonist** binding, mast **cell** activation and therefore inflammation; (ii) palmitoylethanolamide, unlike anandamide, behaves as an endogenous **agonist** for the CB2 receptor on mast cells; (iii) modulatory activities on mast cells exerted by the naturally occurring mol. strengthen a proposed autacoid local inflammation antagonism (ALIA) mechanism; and (i.v.) palmitoylethanolamide and its derivs. may provide antiinflammatory therapeutic strategies specifically targeted mast cells ("ALIAmides").

L10 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:232514 CAPLUS
DOCUMENT NUMBER: 122:23655
TITLE: Anandamide, an endogenous **cannabinoid receptor agonist** inhibits lymphocyte proliferation and induces apoptosis
AUTHOR(S): Schwarz, Herbert; Blanco, Francisco J.; Lotz, Martin
CORPORATE SOURCE: Sam and Rose Stein Institute for Research on Aging and the Department of Medicine, University of California, San Diego, La Jolla, CA, 92093-0663, USA
SOURCE: Journal of Neuroimmunology (1994), 55(1), 107-15
CODEN: JNRIDW; ISSN: 0165-5728
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study examined the immunoregulatory effects of anandamide, the recently identified first endogenous **cannabinoid receptor** ligand. Anandamide caused dose-dependent inhibition of mitogen-induced T and B lymphocyte proliferation. Its potency was 3- and 10-fold less than that of the synthetic cannabinoids Δ8-tetrahydrocannabinol (Δ8-THC) and CP55940, resp. Anandamide effects on DNA synthesis in T and B lymphocytes occurred rapidly as exposure of the cells during the final 4 h of culture was sufficient to achieve >40% inhibition. Low doses of anandamide which caused significant inhibition of lymphocyte proliferation caused DNA fragmentation as demonstrated by immunohistochem., FACS anal. and Southern blotting. Apoptosis was also induced by high concns. of Δ8-THC, but not by CP55940. Brain and **peripheral cannabinoid receptor** mRNA was expressed in PBMC with varying levels between individual donors. These findings demonstrate immunosuppressive effects of anandamide which are associated with inhibition of lymphocyte proliferation and the induction of **cell** death by apoptosis.

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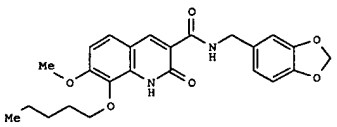
L14 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:57127 CAPLUS
DOCUMENT NUMBER: 142:127582
TITLE: Therapeutic agents for non-immediate **allergy** containing CB2 cannabinoid receptor inverse agonists, identification of candidates of the agents, treatment of non-immediate **allergy** with the inverse agonists, and other use of the therapeutic agents
INVENTOR(S): Iwamura, Hiroyuki; Ueda, Yoshifumi
PATENT ASSIGNEE(S): Japan Tobacco, Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 54 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2005015422	A2	20050120	JP 2003-184496	20030627
PRIORITY APPLN. INFO.:			JP 2003-184496	20030627

GI



I

AB Therapeutic agents containing CB2 (peripheral-type) cannabinoid receptor inverse agonists are useful for treatment of non-immediate **allergic** diseases, e.g. **allergic** dermatitis, asthma, rhinitis, conjunctivitis, etc., and diseases involving **2-arachidonoylglycerol** and/or its ethers, e.g. hematol. cancers, septicemia, circulatory disorders, etc. Candidates of the therapeutic agents are identified by (a) contacting test compds. with cannabinoid receptors and endogenous cannabinoids, (b) measuring binding capacity of the receptors to the endogenous cannabinoids in the presence or absence of the test compds., and (c) selecting compds. capable of decreasing the binding capacity. Thus, oral administration of a dihydroquinolinonecarboxamide derivative I to asthma model mice suppressed immediate asthmatic response, late-phase asthmatic response, and airway hyperresponsiveness. Capsules of I were also formulated.

L14 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L14 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:25545 CAPLUS
DOCUMENT NUMBER: 142:132501
TITLE: New perspectives in the studies on endocannabinoid and cannabis: **2-arachidonoylglycerol** as a possible novel mediator of inflammation
AUTHOR(S): Sugiura, Takayuki; Oka, Saori; Gokoh, Maiko; Kishimoto, Seishi; Waku, Keizo
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Teikyo University, Kanagawa, 199-0195, Japan
SOURCE: Journal of Pharmacological Sciences (Tokyo, Japan) (2004), 96(4), 367-375
CODEN: JPSTGJ; ISSN: 1347-8613
PUBLISHER: Japanese Pharmacological Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. **2-Arachidonoylglycerol** is an endogenous ligand for the cannabinoid receptors. To date, two types of cannabinoid receptors (CB1 and CB2) have been identified. The CB1 receptor is assumed to be involved in the attenuation of synaptic transmission. On the other hand, the physiol. roles of the CB2 receptor, which is abundantly expressed in several types of inflammatory cells and immunocompetent cells, have not yet been fully elucidated. Recently, we investigated in detail possible physiol. roles of the CB2 receptor and **2-arachidonoylglycerol** in inflammation. We found that **2-arachidonoylglycerol** induces the activation of p42/44 and p38 mitogen-activated protein kinases and c-Jun N-terminal kinase; actin rearrangement and morphol. changes; augmented production of chemokines in HL-60 cells; and the migration of HL-60 cells differentiated into macrophage-like cells, human monocytes, natural killer cells, and eosinophils. We also found that the level of **2-arachidonoylglycerol** in mouse ear is markedly elevated following treatment with 12-O-tetradecanoylphorbol 13-acetate, which induces acute inflammation. Notably, the inflammation induced by 12-O-tetradecanoylphorbol 13-acetate was blocked by treatment with SR144528, a CB2-receptor antagonist. Similar results were obtained with an **allergic** inflammation model in mice. These results strongly suggest that **2-arachidonoylglycerol** plays essential roles in the stimulation of various inflammatory reactions in vivo.
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:984101 CAPLUS
DOCUMENT NUMBER: 142:132912
TITLE: **2-Arachidonoylglycerol**, an endogenous cannabinoid receptor ligand, induces the migration of EoL-1 human eosinophilic leukemia cells and human peripheral blood eosinophils
AUTHOR(S): Oka, Saori; Ikeda, Shinobu; Kishimoto, Seishi; Gokoh, Maiko; Yanagimoto, Shin; Waku, Keizo; Sugiura, Takayuki
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Teikyo University, Kanagawa, Japan
SOURCE: Journal of Leukocyte Biology (2004), 76(5), 1002-1009
CODEN: JLBIE7; ISSN: 0741-5400
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **2-Arachidonoylglycerol** (**2-AG**) is an endogenous cannabinoid receptor ligand. To date, 2 types of cannabinoid receptors have been identified: the CB1 receptor, abundantly expressed in the brain, and the CB2 receptor, expressed in various lymphoid tissues such as the spleen. The CB1 receptor has been assumed to play an important role in the regulation of synaptic transmission, whereas the physiol. roles of the CB2 receptor remain obscure. Here, the authors examined whether the CB2 receptor is present in human eosinophils and found that the CB2 receptor is expressed in human peripheral blood eosinophils. In contrast, human neutrophils do not contain CB2 receptors. The authors then examined the effect of **2-AG** on the motility of eosinophils. They found that **2-AG** induces the migration of human eosinophilic leukemia EoL-1 cells. The migration evoked by **2-AG** was abolished in the presence of SR144528, a CB2 receptor antagonist, or by pretreatment of the cells with pertussis toxin, suggesting that the CB2 receptor and Gi/o are involved in the **2-AG**-induced migration. The migration of EoL-1 cells induced by **2-AG** was suggested to be a result of chemotaxis. In contrast to **2-AG**, neither anandamide nor free arachidonic acid elicited the migration. Finally, the authors examined the effect of **2-AG** on human peripheral blood eosinophils and neutrophils and found that **2-AG** induces migration of eosinophils but not neutrophils. Thus, the CB2 receptor and its endogenous ligand **2-AG** may be closely involved in **allergic** inflammation accompanied by the infiltration of eosinophils.
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:640168 CAPLUS
DOCUMENT NUMBER: 137:367010
TITLE: Presence and regulation of the endocannabinoid system in human dendritic cells
AUTHOR(S): Matias, Isabel; Pochard, Pierre; Orlando, Pierangelo; Salzet, Michel; Pestel, Joel; Di Marzo, Vincenzo
CORPORATE SOURCE: Endocannabinoid Research Group, Istituto di Chimica Biomolecolare, Consiglio Nazionale delle Ricerche, Comprensorio Olivetti, Naples, Italy
SOURCE: European Journal of Biochemistry (2002), 269(15), 3771-3778
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cannabinoid receptors and their endogenous ligands, the endocannabinoids, have been detected in several blood immune cells, including monocytes/macrophages, basophils and lymphocytes. However, their presence in dendritic cells, which play a key role in the initiation and development of the immune response, has never been investigated. Here we have analyzed human dendritic cells for the presence of the endocannabinoids, anandamide and **2-arachidonoylglycerol** (**2-AG**), the cannabinoid CB1 and CB2 receptors, and one of the enzymes mostly responsible for endocannabinoid hydrolysis, the fatty acid amide hydrolase (FAAH). By using a very sensitive liquid chromatog.-atmospheric pressure chemical ionization-mass spectrometric (LC-APCI-MS) method, lipids extracted from immature dendritic cells were shown to contain **2-AG**, anandamide and the anti-inflammatory anandamide congener, N-palmitoylethanolamine (PalEtn) (2.1 ± 1.0, 0.14 ± 0.02 and 8.2 ± 3.9 pmol·10-7 cells, resp.). The amts. of **2-AG**, but not anandamide or PalEtn, were significantly increased following cell maturation induced by bacterial lipopolysaccharide (LPS) or the **allergen** Der p 1 (2.8- and 1.9-fold, resp.). By using both RT-PCR and Western immunoblotting, dendritic cells were also found to express measurable amts. of CB1 and CB2 receptors and of FAAH. Cell maturation did not consistently modify the expression of these proteins, although in some cell prepns. a decrease of the levels of both CB1 and CB2 mRNA transcripts was observed after LPS stimulation. These findings demonstrate for the first time that the endogenous cannabinoid system is present in human dendritic cells and can be regulated by cell activation.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:488728 CAPLUS
DOCUMENT NUMBER: 125:117486
TITLE: Formation of antimicrobial electrodeposition films
INVENTOR(S): Kawasaki, Jun
PATENT ASSIGNEE(S): Chugai Mining, Japan; Toshin Kk
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 08120496	A2	19960514	JP 1994-284872	19941118
PRIORITY APPLN. INFO.:			JP 1994-284872 A	19941118
			JP 1994-7549	19940127

AB Title formation, applicable on watches, eyeglasses frames, noble metal-coated bracelets, necklaces, or ear rings, and faucets, involves uniformly dispersing sintered Ca3(PO4)2/**Ag** ceramic particles in electrodepositing resin compns., and co-depositing the particles and resin compns. on articles. A substrate was electrodeposited with a Honnybrite C 1 composition containing 5-10% Apacider AW at 25-75 V to form an uniform coating film with good adhesion, antimicrobial ability and **allergy**-free to human skins.

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     (FILE 'HOME' ENTERED AT 14:54:26 ON 08 SEP 2005)

     FILE 'CAPLUS' ENTERED AT 14:54:37 ON 08 SEP 2005
L1          1383 S INVERSE AGONIST
L2           240 S PERIPHERAL CELL
L3          3336 S CANNABINOID RECEPTOR?
L4          2163 S CANNABINOID RECEPTOR
L5             1 S L1 AND L2 AND L3
L6        101412 S AGONIST
L7          1082 S L6 AND L3
L8          1081 S L7 NOT L5
L9           103 S L8 AND PERIPHERAL
L10           21 S L9 AND CELL
L11         2413 S 2-ARACHIDONOYLGLYCEROL OR 2-AG
L12            2 S (2-ARACHIDONOYLGLYCEROL ETHER) OR 2-AG-E
L13         2413 S L11 OR L12
L14            5 S L13 AND ALLERG?

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---Logging off of STN---


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Executing the logoff script...


=> LOG Y

STN INTERNATIONAL LOGOFF AT 15:01:57 ON 08 SEP 2005
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